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CLIENT ADVISORY

# The FDA Amendments Act of 2007

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On September 27, 2007, the President signed into law legislation that reauthorizes the Prescription Drug User Fee Act (PDUFA IV) and the Medical Device User Fee Act (MDUFA), and makes significant changes to the Food and Drug Administration's (FDA) regulatory framework, with important ramifications for pharmaceutical and medical device companies. The Food and Drug Administration Amendments Act of 2007 (FDAAA, Public Law 110-85) passed the House by a vote of 405 to 7 on September 19, 2007, and the Senate by unanimous consent the following day. The FDAAA is considered the most significant reform of the Federal Food, Drug, and Cosmetic Act (FFDCA) in years.

In addition to reauthorizing PDUFA and MDUFA, the law would reauthorize the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). The law also responds to concerns about drug safety by requiring FDA to establish an active drug risk surveillance system and by granting FDA new powers to require labeling changes and post-market studies, impose legally binding risk management requirements through Risk Evaluation and Mitigation Strategies (REMS), and mandate specific disclosures in direct-to-consumer drug advertisements. The law also creates an expanded national clinical trial registry and results data bank, addresses FDA advisory committee conflicts of interest, and imposes new restrictions on citizen petitions. This client advisory provides a broad summary of the key provisions of the legislation. Future client advisories will address specific aspects of FDAAA in greater detail.

## I. PDUFA IV [TITLE I]

Title I of the FDAAA reauthorizes the PDUFA, which was set up to expire on September 30, 2007. User fees collected under the law are to be dedicated toward expediting the drug development process and the process for the review of human drug applications, including post-market drug safety activities, as set forth in performance goals agreed to by FDA and documented in correspondence from FDA to the relevant congressional committees. Although some early opposition to PDUFA reauthorization surfaced, claiming that user fee funding of the drug review process created an inappropriate industry-agency relationship, budget realities resulted in little support for this view. The law not only reauthorizes PDUFA, but extends it into areas beyond the legislation's original mandate of providing resources for the review of new drug applications.

The law raises fee revenue amounts to $392.8 million for fiscal year 2008 and includes adjustment methods for fiscal years 2009-2012. It also provides for an additional $225 million in fees for fiscal years 2008 through 2012 for post-market drug safety activities. The legislation includes a new exemption from product and establishment fees for orphan drugs.

The law expands FDA's use of user fee funding to include collecting, developing, and reviewing safety information (including adverse event reports), developing and using adverse event data collection systems (*e.g.*, IT systems), developing and using improved analytical tools to assess potential safety problems (*e.g.*, external data banks), and complying with other requirements related to post-approval studies, clinical trials, and labeling changes. The FDAAA removes the PDUFA III limitation of three years on use of user fee monies for post-market drug safety activities.

The law for the first time authorizes FDA to assess and collect user fees for providing advisory reviews of direct-to-consumer (DTC) television advertisements. This fee will apply only to voluntary manufacturer requests for pre-dissemination review of DTC advertisements; mandatory pre-market reviews under Title IX of the law will not be subject to the fee unless the manufacturer designates the advertisement for advisory review. A manufacturer must specify in advance how many advertisements it anticipates submitting in the course of the next fiscal year and must pay an up-front fee for the number of reviews requested. Should the manufacturer submit more advertisements for review than in its original estimate, the per-advertisement fee for the additional reviews will be increased by 50%.

The fiscal year 2008 fee limit is $83,000, with a capped 50% increase for each successive fiscal year. If the program does not receive a minimum level of funding (at least $11.25 million in year one, and $9 million in later fiscal years) within 120 days of enactment or the start of the new fiscal year, the program will not commence and all fees will be refunded.

The formulation of FDA's performance goals for the next reauthorization of PDUFA (PDUFA V) will require greater public participation and transparency. The FDAAA requires that before FDA begins negotiations with industry, the Secretary must publish notice in the *Federal Register* requesting the public's input and hold a meeting to provide the public with an opportunity to present its views. For a 30-day period following the meeting, the Secretary will receive public comments and publish the comments on FDA's website. Moreover, once each month during negotiations, the Secretary will consult with representatives from patient and advocacy organizations. After the PDUFA V negotiations with industry conclude, the Secretary will post the minutes of the negotiation meetings on FDA's website. The Secretary will also present the recommendations to the congressional committees of jurisdiction, publish the recommendations in the *Federal Register* (providing for a 30-day comment period), hold a public meeting, and then revise the recommendations as necessary.

## II. MDUFA [TITLE II]

Congress created a medical device user fee framework in 2002, and the FDAAA reauthorizes the fees for the first time. The law preserves existing fee categories and establishes three new types of fees. The first, an annual establishment registration fee, begins in fiscal year 2008. The second is an annual fee for filing periodic reports required by a pre-market application (PMA) approval order concerning a class III device. The third is a fee for a 30-day notice – a request to make modifications to manufacturing procedures or methods of manufacture affecting the safety or effectiveness of a device. Starting in fiscal year 2008, the legislation would generally increase fees by 8.5% each year. The law authorizes $7.1 million in additional device post-market safety activities in fiscal year 2008, with annual increases escalating to more than $8.6 million by fiscal year 2012. The current restriction that fees may not be assessed if the amount of medical device-related direct appropriations falls below a specified threshold is extended through fiscal year 2012. The law also contains

transparency provisions similar to those under Title I; these provisions will apply to the next reauthorization of the MDUFA.

The law incorporates a number of changes intended to expand participation in the third-party inspection program. The reauthorization deems eligible firms that notify FDA of their intent to use an "accredited party" for an inspection to have clearance to proceed with such an inspection unless the Secretary affirmatively denies the clearance within 30 days due to a false certification regarding the device, a compliance problem, or the rejection of the third-party inspector. The FDAAA also allows device manufacturers to submit to FDA audit reports assessing compliance with quality system standards set by the International Organization for Standardization (ISO) and identified by the Secretary in a public notice. Such submissions are intended to assist FDA in setting risk-based inspectional priorities.

The FDAAA requires that the Secretary promulgate regulations to establish a unique device identification system. The regulations must require that medical devices include a unique identifier in their labeling, unless the Secretary determines an alternative place for the identifier or provides an exception for a certain device or type of device. The unique identifier is to identify the device through distribution and use.

The law also requires a study by the Government Accountability Office (GAO) on the appropriate use of the "510(k)" pre-market notification process.

## III. PEDIATRIC MEDICAL DEVICE SAFETY AND IMPROVEMENT ACT OF 2007 [TITLE III]

FDAAA seeks to encourage pediatric medical device research, to enhance the safety of those products and encourage the manufacture of special pediatric medical devices. The law requires PMA and Humanitarian Device Exemption (HDE) applicants to include in their applications a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to address. It also requires the Secretary, within 18 months of enactment, to report to Congress on the number of such pediatric devices approved in the preceding year, the number of devices approved in the preceding year labeled for pediatric patients, the number of pediatric devices approved in the preceding year that are exempted from a user fee pursuant to pediatric conditions of use, and the products' review times.

Under some circumstances, the FDAAA allows a manufacturer of a pediatric device legally distributed under an HDE to sell the device for a profit. The law also expands current device surveillance authorities by permitting the Secretary to require prospective surveillance of more than 36 months or post-market surveillance for any class II or class III device expected to have significant use in pediatric populations.

Further, the law requires that within 180 days the Secretary must submit a plan for expanding pediatric medical device research and development. The plan must include the current status of federally funded pediatric medical device research, any gaps in pediatric medical device research, a research agenda for improving pediatric medical device development and clearance or approval, and a plan for evaluating the short- and long-term safety and effectiveness of pediatric medical devices.

Within 90 days of enactment, the Secretary must issue a request for proposals for one or more grants or contracts to nonprofit consortia for projects designed to promote pediatric device development. The law authorizes $6 million for each fiscal year 2008 through 2012 for this purpose. A nonprofit consortium that receives a grant or contract under this section will facilitate the development, production, and distribution of pediatric medical devices by encouraging innovation and connecting individuals with pediatric device ideas with potential manufacturers. Each consortium that receives a grant or contract will report each year to the Secretary on the status of pediatric medical device development, production, and distribution that has been facilitated by the consortium.

## IV. PEDIATRIC RESEARCH EQUITY ACT OF 2007 [TITLE IV]

The law reauthorizes the Pediatric Research Equity Act (PREA). While the House bill would have eliminated the sunset on PREA, the law maintains the sunset, so the law will now expire in 2012.

Under the PREA, a new drug application or supplement must be accompanied by a pediatric assessment. If the assessment indicates that the treatment for the disease has a similar course in all adult and pediatric populations, the Secretary may conclude that data supporting pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults or from one pediatric age group to another.

In addition, FDAAA significantly expands the PREA's procedures for deferring pediatric assessments. In order for an applicant to obtain a deferral, the applicant must submit a timeline for completion of pediatric studies. Following a deferral, the applicant will provide the Secretary each year with information detailing the progress made in conducting the studies, and if no progress has been made, evidence and documentation that such studies will be conducted with due diligence at the earliest possible time. The information will be available to the public through FDA's website.

The Secretary retains the power to grant a full or partial waiver from the PREA assessment for good cause. However, when an applicant states that a waiver is required because a pediatric formulation is not possible, applicants are now required to submit to the Secretary documentation detailing why a pediatric formulation cannot be developed. If the waiver is granted, the applicant's submission will be made public on FDA's website.

One of the grounds for a good cause waiver is that a drug or biological product does not represent a "meaningful therapeutic benefit" over existing therapies for pediatric patients. The law amends the definition of "meaningful therapeutic benefit" to make it easier for the Secretary to find that a product does represent such a benefit. The definition requires the Secretary to determine whether the approved drug or biologic could represent an improvement in the treatment, diagnosis, or prevention of a disease compared with marketed products adequately labeled for that use in the relevant pediatric population. Previously, the Secretary was required to find a "significant improvement" for a product to represent a meaningful therapeutic benefit over existing therapies.

The FDAAA also formalizes dispute resolution procedures followed when FDA requests a labeling change to incorporate pediatric information. If the sponsor disputes the proposed change and the FDA Commissioner and sponsor are unable to reach an agreement on the appropriate changes to the labeling for the drug, then not later than 180 days after the date of the submission, the Commissioner will request that the sponsor make any labeling change that the Commissioner determines to be appropriate. If the sponsor does not agree within 30 days to make the requested change, the Commissioner will refer the matter to the Pediatric Advisory Committee. Within 90 days of receiving the referral, the Pediatric Advisory Committee will review the pediatric study reports and make a recommendation to the Commissioner. Within 30 days of receiving the Pediatric Advisory Committee's report, the Commissioner will make a renewed request for a labeling change. If the sponsor does not agree to make a labeling change, the Commissioner may deem the drug to be misbranded.

Not later than 210 days after the date of submission of a pediatric assessment, the Secretary must make available medical, statistical, and clinical pharmacology reviews on FDA's website. Sponsors of assessments that result in labeling changes are required to distribute such information to physicians and healthcare providers. In addition, sponsors must submit all adverse event reports connected to the labeling change to the Office of Pediatric Therapeutics. FDA will also make public an annual report of all such labeling changes.

The FDAAA requires the Institute of Medicine (IOM), within three years, to study and review the use of extrapolation for

pediatric subpopulations, the use of alternative endpoints for pediatric populations, neonatal assessment tools, the number and types of pediatric adverse events, and ethical issues in pediatric clinical trials.

## V. BEST PHARMACEUTICALS FOR CHILDREN ACT OF 2007 [TITLE V]

The law reauthorizes the Best Pharmaceuticals for Children Act of 2007 (BPCA) for an additional five years. The BPCA grants an additional six months of marketing exclusivity in exchange for pediatric research. FDAAA does not include the reduction from six to three months of exclusivity for "blockbuster" drugs that had been included in the Senate bill. The FDAAA also expands the definition of pediatric studies to include pre-clinical studies at the discretion of the Secretary.

Current law requires that, if the Secretary makes a written request for pediatric studies, the applicant must respond within 180 days. Under the FDAAA, if the applicant does not agree with the request on the grounds that a pediatric formulation cannot be developed, the applicant must provide an explanation why such a formulation cannot be developed. Within 180 days of receiving the report, the Secretary will accept or reject the determination. The Secretary must publish a notice of any determination made on or after enactment and will identify any drug for which a pediatric formulation has been developed. The Secretary will make available on FDA's website the number of studies conducted, the specific drugs and drug uses, the types of studies conducted, the number of pediatric formulations developed, the number of pediatric formulations not developed and the reasons why, and the labeling changes made as a result of studies.

If the pediatric studies for a drug have not been completed, and a continuing need for the information persists, the Secretary is to make a determination regarding whether an assessment will be required. The Secretary has 30 days before making this determination to certify whether the Foundation for the National Institutes of Health (NIH) has adequate funding to fund all of the studies. For a drug with no listed patents or with an expired patent (or patents), the Secretary will refer the drug for inclusion on the list of drugs for which pediatric studies are needed and for which grant funding will be made available by the NIH.

The new law will also require an IOM study on the written requests made and the studies conducted under the BPCA requirements. The study will review and assess representative samples of requests and studies and make recommendations regarding appropriate incentives for encouraging pediatric studies of biologics.

## VI. REAGAN-UDALL FOUNDATION AND CRITICAL PATH PARTNERSHIPS [TITLE VI]

The legislation establishes the Reagan-Udall Foundation (Foundation), a nonprofit corporation to advance the mission of FDA to modernize medical product development, accelerate innovation, and enhance product safety. The Foundation will be responsible for "taking into consideration the Critical Path reports and priorities," identifying unmet needs, and establishing goals in drug and device development, manufacture, and approval. This would include awarding grants and contracting with other nonprofit organizations, academic institutions, scientists (including at FDA), and industry.

The Foundation would also be responsible for providing "objective clinical and scientific information" to FDA and other federal agencies upon request. This information-sharing function extends to permitting federal employees to serve on advisory committees to the Foundation and to work at the Foundation for certain periods of time.

Most of the funding for the Foundation will come from private sources. While the legislation authorizes FDA to transfer between $500,000 and $1.25 million to the Foundation each year, it gives the Executive Director the authority to solicit and accept funds and gifts on behalf of the Foundation.

The FDAAA would also establish critical path public-private partnerships. The Secretary would be authorized to enter into collaborative agreements, "Critical Path Public-

Private Partnerships," with private entities to implement the Critical Path Initiative. Eligible entities are academic institutions and nonprofit organizations with expertise in biomedical science. The entities must be able to develop and evaluate methods to increase efficiency of medical product development, more accurately identify benefits and risks of existing products, establish partnerships (*e.g.*, with healthcare providers, consumers, and manufacturers), and obtain funding from federal and private sources. The law authorizes $5 million for fiscal year 2008 for this purpose and such sums as necessary for each subsequent year through 2012.

## VII. CONFLICTS OF INTEREST [TITLE VII]

This Title would restrict the Secretary's ability to grant waivers to permit participation of persons with financial conflicts of interest in advisory committee meetings. Unlike the earlier House bill, which would have allowed the Secretary to grant just one waiver per advisory committee meeting, the law requires the Secretary to determine the aggregate percentage of waivers provided in fiscal year 2007. Thereafter, the Secretary must decrease the number of waivers by 5% each fiscal year from 2008 to 2012. The Secretary must disclose all waivers on FDA's website. FDAAA also requires the Secretary to report to Congress on the number of advisory committee vacancies and nominations, the number of disclosures required, and a plan for how the Secretary plans to reduce the number of vacancies.

## VIII. CLINICAL TRIALS [TITLE VIII]

The law would direct the Secretary, acting through the Director of NIH, to expand NIH's existing clinical trials registry (clinicaltrials.gov). It expands the types of drug trials that must be registered, extends registration requirements to medical devices, and establishes new results reporting rules.

### *A. Registry*

For all post-Phase I drug trials and trials comparing a medical device against a control or conducted for pediatric post-market surveillance purposes, the responsible party (*e.g.*, the sponsor or principal investigator) must submit the following information for inclusion in the registry data bank:

1. Descriptive information about the trial (a title intended for the public, a summary for the public, the primary purpose, the study design, the study phase of a drug trial, the study type, the primary disease or condition being studied, the intervention name and type, the study's start date, the expected completion date, the target number of subjects, and primary and secondary outcomes);
2. Recruitment information (including eligibility criteria, overall recruitment status, individual site recruitment status, and information about expanded access to the drug);
3. Location and contact information (including the name of the sponsor, the responsible party, and the facility name and contact information); and
4. Administrative data (including unique protocol identification number, other protocol identification numbers, and the FDA IND/IDE protocol number).

The Secretary may modify these requirements.

The registry data bank must be searchable by disease or condition, name of the intervention, location, age group, study phase, sponsor, recruitment status, the National Clinical Trial number or other identification, and "safety issue." The format of the registry must make it easy for the public to use and provide for easy comparison between entries.

The responsible party for a trial must submit required study data to NIH by the later of 90 days from enactment, 21 days after the first patient is enrolled, or one year for trials that are ongoing on the date of enactment. The Director of NIH must post the registration information for a drug trial within 30 days of its submission. For a trial of a device that has not yet been approved, the Director must post the submitted information after or on the date of the device's approval but no later than 30 days from that date. For a previously approved device, the Director has one year and 30 days from enactment to post the information.

### *B. Results Data Bank*

The law requires that the Secretary expand the registry data bank to include the results of the trials that form the primary basis of an efficacy claim or are conducted after approval. These results are to be made publicly available on the Internet and with a glossary of technical terms. The White House had opposed any inclusion of a results data bank in the law, as well as the posting of results online.

The results data bank must include links to the following information related to covered trials:

1. FDA summary documents, if an advisory committee considered an applicable clinical trial;
2. Any assessments of the results for pediatric studies or research;
3. FDA public health advisories;
4. The action package for approval document (for an applicable drug trial);
5. The detailed summary of information on the safety and effectiveness of the device or the 510(k) summary of the data (for an applicable device trial); and
6. NIH information (Medline citations and the entry for the drug in the National Library of Medicine data bank, if available).

The Secretary may also include these links for clinical trials submitted prior to enactment. Within one year of enactment, the registry and results data bank will also include demographic and baseline information to describe the patients who participated in the trial, the primary and secondary outcomes, a point of contact about the trial results, and whether there are any agreements between the sponsor and the principal investigator that restrict the ability of the principal investigator from discussing or publishing the results. Responsible parties also must submit periodic updates to the registry and results data bank.

The law provides for the Secretary to further expand the registry and results data bank through a rulemaking that must occur no more than three years after enactment. The expanded results data bank would require the inclusion of:

1. A non-technical summary of the trial and its results for patients, if the Secretary determines that these summaries can be non-promotional and not misleading;
2. A technical, non-promotional summary, if the Secretary determines that these summaries can be non-promotional and not misleading;
3. The trial's protocol; and
4. Other categories the Secretary determines to be appropriate.

The inclusion of trial results summaries in language that patients can understand was a particularly controversial provision, with the White House arguing that such summaries would present a high likelihood for bias and consumer advocates asserting the summaries were essential for the public to understand drug research. The final language is a compromise between those two positions.

While the clinical trials for approved products would be required to be included in the results data bank, the Secretary would determine through regulations whether to also include trials for unapproved products. The Secretary is also to determine through rulemaking the timeline for submitting the results and updates, as well as procedures for quality control, a standard format for submission of information, and additional information on trials and results written in a non-technical manner. The Secretary will also consider the World Health Organization's consensus data elements for clinical trial results and will hold a public meeting to provide an opportunity for interested individuals to provide input on the regulation.

The Secretary is to use the rulemaking process to determine the best method for including adverse event information in the registry and results data bank in a way that is not misleading to patients or doctors. The law includes default elements related to adverse events, however, if the Secretary does not issue a regulation 24 months after enactment. The Secretary would include in the registry and results data bank a table of anticipated and unanticipated serious and frequent adverse events.

For clinical trials that are completed before the drug or device is approved or the device is cleared, the responsible party must submit the trial results no more than 30 days after approval or clearance. For trials that are conducted for the purpose of seeking an approval for a new use of the drug or device, the responsible party must submit the results 30 days after the date the new use is approved, licensed, or cleared; the Secretary issues a letter to not approve or clear the submission; or the application is withdrawn. The Director may approve an extension of the submission deadline if the responsible party submits a written request showing good cause for the extension. The Secretary may waive any requirement if a responsible party makes a written request and the Secretary determines that extraordinary circumstances justify the waiver. If the Secretary grants a waiver, he or she must also notify the appropriate congressional committees.

All clinical trials that receive grant money from the federal government must be the subject of a certification by the responsible party that all of the required registry and data bank submissions have been made to NIH. This information is then verified with the head of the federal agency from which the grant comes. The certification will be submitted to FDA along with an application for marketing approval.

If the responsible party for a trial does not submit required clinical trial information, or submits information that is false or misleading, notice of that violation will be publicly posted in the database.

The law creates civil penalties for failure to comply with its requirements. A maximum amount of $10,000 would be imposed for a violation. If the violation is not corrected in 30 days, then a penalty of $10,000 for each day of the violation would be assessed until it is corrected.

Finally, the law would preempt any state law requiring the registration of clinical trials or the disclosure of their results.

### *IX. Post-Market Studies and Clinical Trials; Labeling [Title IX]*

FDAAA provides FDA with new authority to require post-approval studies or clinical trials, as well to require labeling changes for approved drug products. The Secretary will now have the authority to require a post-approval study or clinical trial of a drug to assess a known serious risk, or signals of a serious risk, and to identify an unexpected serious risk. Studies or trials are only to be required if the Secretary determines that current reporting and the post-market risk identification analysis system are not sufficient to address the concern. A clinical trial may not be required if a post-approval study is sufficient. For each required study or trial, the Secretary will require a timetable for its completion and periodic reports on status. A responsible person may appeal a requirement under FDA's normal dispute resolution procedures.

If the Secretary becomes aware of new safety information that he or she believes should be included in a drug's labeling, the Secretary must notify the holder of the approved application. The new safety information can be derived from clinical trials, post-approval studies, peer-reviewed biomedical literature, or post-market risk identification and analysis systems data. Within 30 days of the notification, the holder must submit a supplement proposing labeling changes or notify the Secretary that he or she does not believe labeling changes are warranted and why. If the Secretary disagrees with the proposed changes or notification that labeling changes are not warranted, the Secretary will initiate discussions with the holder (not to extend beyond 30 days). Within 15 days of the conclusion of the discussions, the Secretary may issue an order directing the responsible person or holder to make a labeling change, and the responsible person or holder then has 15 days to submit a supplement with the labeling change. Within five days of receiving an order, a holder or responsible person may appeal using FDA's normal dispute resolution procedures.

The law includes a "rule of construction," the product of lobbying by the plaintiffs' bar, that attempts to leave it to the courts to address the preemptive effect of FDA labeling actions. While earlier versions of the legislation in the

House contained language asserting that the legislation would not preempt state law, the final "rule of construction" states:

> This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including Subpart B of Part 201 and Section 314.70 and 601.12 of Title 21, Code of Federal Regulations (or any successor regulations).

This "rule of construction," while undoubtedly a tool that will be used by plaintiffs seeking to undermine preemption in "failure to warn" cases, makes little sense in that it is inconsistent with the specific labeling change and REMS provisions in FDAAA and attempts to elevate a regulation to statutory status. Moreover, FDAAA did not overturn FDA's preemption policy statement providing the agency's interpretation of the preemptive effect of FDA labeling authorities and the meaning of the referenced "changes be effected" (CBE) regulation.

## X. RISK EVALUATION AND MITIGATION STRATEGIES (REMS) [TITLE IX]

The legislation provides a statutory framework for integrating "risk evaluation and mitigation strategies" (REMS) into drug reviews and post-market pharmacovigilance. The current proposals are an evolution from PDUFA III, which provided funding for development of FDA risk-management guidances and review of voluntary risk minimization plans. Many of the risk minimization tools in the legislation are already in use in existing drug approvals (*i.e.*, under Subpart H/Risk Minimization Action Plans (RiskMAPs)).

Unlike the earlier Senate bill, the compromise does not impose a REMS on all drugs and biologics prior to approval. Under the law, the Secretary (in consultation with the office responsible for reviewing the drug and the office responsible for the drug's post-approval safety) may determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. The Secretary may also require a REMS for new drug and biologic license applications, drugs and biologics that have already been approved, and for supplemental applications seeking approval of a new indication. The holder of a covered application has 120 days to submit its proposed REMS from the time it is notified by the Secretary.

A REMS must include a timetable for the submissions of assessments of the REMS (assessments after 18 months, three years, and seven years, although the Secretary may eliminate assessments after the three-year period if the serious risks of the drug are being adequately managed). Additional elements may also be required by the Secretary: (1) a medication guide and/or patient package insert for distribution to patients and (2) a communication plan to healthcare providers (*e.g.*, sending letters, disseminating information to healthcare providers directly or though professional organizations).

The Secretary may also require "such elements as are necessary" to assure a drug's safe use if, because of its "inherent toxicity or potential harmfulness," it is associated with a serious adverse drug experience and could be approved only if (or withdrawn unless) the elements are made part of the REMS. These elements are to be commensurate with the drug's risk; be publicly posted, with an explanation by the Secretary, within 30 days of the date it is imposed; conform with elements of other drugs with similar serious risks; and be designed to be consistent with established systems for distributing and dispensing drugs. The elements are not to be unduly burdensome on patient access, especially with respect to patients with serious or life-threatening diseases or conditions, or patients who have difficulty accessing healthcare. The elements must include one or more goals to mitigate a specific risk listed in the drug's labeling and may require that:

1. Prescribers have certain training or certification;
2. That settings that dispense the drug are certified;
3. That the drug only be dispensed to patients in certain settings (*e.g.*, hospitals);
4. The drug be dispensed with documentation of safe-use conditions (*e.g.*, laboratory tests);

5. The patient be subject to monitoring; or

6. Each patient using the drug be enrolled in a registry.

The elements may also include a system in which the applicant would be required to take reasonable steps to monitor, evaluate, and improve implementation of required elements by providers and other parties in the healthcare system responsible for implementing the elements. The law provides a waiver of these requirements for a qualified countermeasure in the case of a public health emergency.

Under the new law, the Drug Safety and Risk Management Advisory Committee will seek input from patients and providers about the elements, as well as evaluate the elements of at least one drug, to ensure access and minimize the burdens. The Committee would also use the input and evaluations to issue guidance and modify elements.

A drug that is subject to an abbreviated new drug application (ANDA) is subject to the elements of a medication guide or patient package insert for the applicable listed drug and elements to assure safe use if required for the listed drug. The Secretary may waive the requirement that the drug subject to the ANDA use the same single, shared system as the listed drug if the burden of creating a shared system outweighs its benefits or if an aspect of the elements for the listed drug is claimed by a patent or process and the applicant for the ANDA certifies that it has sought a license for use of an aspect of the elements but was unable to obtain one.

A responsible person must submit an assessment of a REMS when submitting a supplemental application for a new indication, when required by the REMS timetable, and when required by the Secretary on the basis of new safety or efficacy data. Assessments for approved REMS must include an evaluation of how the elements are meeting the goal of safe use, as well as the status of any required post-approval study or clinical trial. FDAAA would deem a drug to have a REMS if there are already elements to assure safe use in place (*i.e.*, 21 C.F.R. §§ 314.520 or 601.42 "approval with restrictions to assure safe use") or otherwise agreed to by the Secretary and the applicant.

The Secretary, in consultation with the office reviewing the drug or responsible for post-approval studies, must promptly review all proposed REMS and each assessment of an approved REMS. No later than 60 days from the REMS' submission (or 30 days if the Secretary determines there may be cause for withdrawal of the drug), the Secretary must initiate discussions with the responsible person. The Secretary will either describe any required REMS as part of the action letter on the application or issue an order within 90 days of beginning discussions. Any action letter or order will be made publicly available.

When a concern about a serious risk of a drug may be related to that drug's pharmacological class, the Secretary may defer assessments of the approved REMS until having convened one or more public meetings to consider responses to the class-based concern. The Secretary must provide notice of the deferral to the holder within five days, publish notice in the *Federal Register*, and publish notice of any public meetings. The meetings may include discussion with the responsible person, meetings of advisory committees, or workshops of scientific experts and other stakeholders. After considering the discussions in the meetings, the Secretary may announce a planned regulatory action in the *Federal Register*, seek public comment, and then issue an order.

FDAAA also sets up REMS dispute resolution procedures. If the REMS was submitted at initial approval and there is a dispute about it, then major dispute resolution procedures previously established under PDUFA and FDA guidance would apply. For all other disputed REMS, the responsible person may request that the Drug Safety Oversight Board (DSOB) review the dispute. The DSOB will be composed of federal employees who are scientists and healthcare practitioners and appointed by the Secretary and will meet at least once each month. Although a determination by the Secretary that a REMS is required is not subject to review, the particular elements of a REMS may still be reviewed.

Under this procedure, the Secretary must publish notice that a dispute is to be reviewed by the DSOB. Entering into dispute resolution does not preclude further discussions or the use of FDA's administrative appeals, although the responsible person must either withdraw the request for review or terminate the use of administrative appeals.

Both parties make a written or oral presentation to the DSOB. The meeting is to be recorded and then made public within 90 days. The DSOB may add members with relevant experience from FDA or other public health agencies for a meeting. No more than five days after the meeting, the DSOB will provide a written recommendation to the Secretary on how to resolve the dispute. The recommendation must also be made public. The Secretary must issue an action letter or order that resolves the dispute before the action deadline for the action letter on the application or seven days after receiving the DSOB recommendation.

A drug will be considered misbranded if the responsible person does not comply with a REMS requirement. The law establishes civil monetary penalties of $250,000 per violation, not to exceed $1 million. If a violation continues after the Secretary provides written notice to the responsible person, a civil monetary penalty of $250,000 for the first 30-day period may be imposed, doubling for each subsequent 30-day period, not to exceed $1 million in a 30-day period and $10 million for all violations adjudicated in a single proceeding. The $10 million maximum penalty is a reduction from the $50 million figure in the House bill.

FDAAA requires that the Commissioner report to Congress on how best to communicate to the public the risks and benefits of new drugs. The Commissioner may consider the possibility of using a symbol indicating that the drug was recently approved in the labeling and in any DTC advertisements.

## XI. DIRECT-TO-CONSUMER (DTC) ADVERTISING [TITLE IX]

The FDAAA authorizes the Secretary to require the submission of any television advertisement for review 45 days before it is aired. The Secretary may recommend, but may not make or direct, changes that are necessary to protect consumers or consistent with the prescribing information under review. Also, if it is appropriate and information exists, the Secretary may recommend statements to address specific efficacy as it relates to certain groups (*e.g.*, the elderly, children, and racial and ethnic minorities).

FDAAA authorizes the Secretary to require specific disclosures in such ads. If the Secretary determines that a television advertisement would be misleading unless it includes a disclosure about a serious risk listed in the drug's labeling, the Secretary may require its inclusion.

FDAAA would also require that any DTC television or radio advertisement present the major statement relating to the drug's side effects in a clear, conspicuous, and neutral manner. Within 30 months of enactment, the Secretary must promulgate regulations establishing standards for whether a major statement is presented in such a manner.

Manufacturers would be subject to civil penalties for disseminating a false or misleading DTC advertisement. The law caps the amount at $250,000 for the first violation in a three-year period and $500,000 for each subsequent violation in a three-year period. The law also provides an opportunity for a hearing, which includes consideration of whether the person submitted the advertisement for pre-review and incorporated the Secretary's comments. No person will be subject to the penalties if he or she submitted the advertisement to the Secretary and incorporated each of the Secretary's comments. While the Secretary may retract or modify comments based on new information, the Secretary must also then provide the person with the new views and a reasonable time to make any modifications.

Within two years of enactment, the Secretary will report to Congress on DTC advertising and its ability to communicate to certain groups (*e.g.*, elderly, children, and racial and ethnic minorities). The Secretary would use the Advisory Committee on Risk Communication that is established

by the law to study DTC advertising's effect on access to health information and decreased health disparities and to make a recommendation on how to present and disseminate information. The report will also include recommendations on impediments to participation in clinical trials for the elderly, children, racially and ethnically diverse populations, and underserved communities.

The FDAAA also includes a provision that requires published DTC communications to contain the text "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088." This is in contrast to the earlier House version that would have required the language in all DTC advertisements. The Secretary, in consultation with the Advisory Committee on Risk Communication, would also have to study whether this statement is appropriate for inclusion in television advertisements.

## XII. POST-MARKET RISK IDENTIFICATION AND ANALYSIS [TITLE IX]

Within two years of enactment, the Secretary will, in collaboration with the public, academics, and private entities, develop methods to obtain access to different data sources and validated methods for the establishment of a post-market risk identification and analysis system to link and analyze data from multiple sources. The goals of the collaboration include linking to safety data from at least 25 million patients by July 2010 and 100 million by July 2012. The law would also require the Secretary to convene a committee of experts to make a recommendation on the development of tools and methods for the communication of post-marketing data.

One year after developing the methods, the Secretary must establish and maintain procedures for the post-market risk identification and analysis system:

1. For risk identification and analysis in compliance with Health Insurance Portability and Accountability Act of 1996;
2. For the reporting of data on all serious adverse drug experiences;
3. To provide for active adverse event surveillance using federal health-related electronic data (*e.g.*, Medicare and the Department of Veterans Affairs health systems), private sector health-related electronic data (*e.g.*, pharmaceutical purchase data and health insurance claims), and other data the Secretary deems necessary;
4. To identify trends and patterns;
5. To provide regular reports to the Secretary concerning adverse event trends; and
6. To enable the program to export data for further aggregation and analysis.

The Secretary will establish collaborations with public, academic, and private entities (which may include the Centers for Education and Research on Therapeutics (CERTS)) to provide for advanced analysis of drug safety data. At least twice each year, the Secretary will seek recommendations from the Drug Safety and Risk Management Advisory Committee and other advisory committees regarding priority drug questions. The law would permit the Secretary to contract with private entities to develop this information.

The Secretary must conduct bi-weekly screenings of the Adverse Event Reporting System (AERS) database and post a quarterly report on the AERS website regarding any new safety information. FDAAA also requires the Secretary to review the backlog of post-market safety commitments each year to determine which safety commitments require revision or should be eliminated, and report to Congress on these determinations.

Finally, the law requires several additional reports. First, the Secretary must report to Congress within four years of enactment on the ways the Secretary has used the post-market risk identification and analysis system to identify specific drug safety signals and to better understand the outcomes associated with marketed drugs. The Secretary must also report to Congress within two years of enactment on FDA's procedures to address ongoing post-market safety issues identified by the Office of Surveillance and Epidemiology. Additionally, the GAO must report on

data privacy issues associated with the post-market risk identification and analysis system and whether there is a need for additional legislative actions to ensure patient privacy.

## XIII. ANTICOUNTERFEITING [TITLE IX]

The law requires that the Secretary establish standards and identify effective technologies to secure the drug supply chain against counterfeiting. In consultation with federal agencies (including the Department of Justice, the Department of Homeland Security, and the Department of Commerce), manufacturers, distributors, pharmacies, and other supply chain stakeholders, the Secretary will prioritize and develop these standards for identification and tracking and tracing of drugs.

Within 30 months of enactment, the Secretary must develop a standardized numerical identifier (harmonized with international consensus standards, to the extent practicable). The numerical identifier is to be applied at the site of manufacturing and repackaging at the package or pallet level and must be able to identify, validate, authenticate, and track and trace the drug. The legislation identifies promising technologies that must be addressed by the Secretary and may include radio frequency identification technology (RFID), nanotechnology, encryption technologies, and other track and trace or authentication. FDAAA also requires the Secretary to expand and enhance enforcement against counterfeiting and establish regional capacities for the validation and inspection of prescription drugs.

## XIV. CITIZEN PETITIONS [TITLE IX]

FDAAA seeks to make it harder to obtain review of citizen petitions that may impact the entry of generics onto the market. Under the law, the Secretary may not delay approval of a pending ANDA or 505(b)(2) application because of a citizen petition, unless the delay is necessary to protect the public health. If the Secretary determines that the primary purpose of a petition is to delay the approval of an application and the petition does not raise valid scientific or regulatory issues, the Secretary may deny the petition. The Secretary may issue guidance with the factors the Secretary uses to make this determination.

The Secretary is required to take final agency action on a petition no more than 180 days after it was filed and may not extend the 180 day period for any reason. If the Secretary fails to act on a petition within 180 days, such failure to act constitutes final agency action. If a civil action is filed against the Secretary before the Secretary has taken final agency action, the court must dismiss the suit for failure to exhaust administrative remedies.

All petitions would have to include a certification stating that the petition contains all unfavorable information known to the petitioner and the amount of any payments the person received to file it. Any supplemental information and comments must also include a verification that the person did not intentionally delay the submission of the information.

Each year, the Secretary will report to Congress on the number of ANDA and 505(b)(2) applications approved, the number of such applications delayed by petitions, the number of days those petitions were delayed, and the number of petitions submitted. The Secretary is also required to report to Congress one year after enactment on ways to encourage the early submission of petitions.

## XV. ANTIBIOTICS AND ENANTIOMERS [TITLE XI]

The law contains a number of provisions related to antibiotics, but not the earlier Senate language that would have granted exclusivity to "old antibiotics" approved before November 21, 1997. Among the antibiotics provisions in the law is a requirement that the Secretary issue guidance for antibiotic clinical trials and to review that guidance within five years.

FDAAA would also require FDA to identify "clinically susceptible concentrations"[1] of antimicrobials and make that information available publicly within 30 days. It would also require the Commissioner to hold a public meeting on incentives to encourage the development of antibiotics to

[1] Clinically susceptible concentrations are defined as "specific values which characterize bacteria as clinically susceptible, intermediate, or resistant to the drug (or drugs) tested."

treat orphan diseases. The law would authorize $30 million for grants under the Orphan Drug Act to study antibiotics.

The law also provides that for new drug applications for a non-racemic drug containing as an active ingredient a single enantiomer that is contained in a racemic drug approved in another new drug application, the applicant may choose to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug (*e.g.*, FDA may consider it to be a new chemical entity eligible for five-year Hatch-Waxman exclusivity). This election, however, may only be made if:

1. The single enantiomer has not been previously approved except in the approved racemic drug;
2. The new drug application for such non-racemic drug includes full reports of new clinical investigations and does not rely on any investigations that are part of an application submitted for approval of the approved racemic drug; and
3. The new drug application for such non-racemic drug is not submitted for approval of a condition of use in a therapeutic category in which the approved racemic drug has been approved or for which any other enantiomer of the racemic drug has been approved.

If the sponsor chooses to take advantage of this provision, then the Secretary may not approve such non-racemic drug for any condition of use in the therapeutic category for which the racemic has been approved until ten years from the date the non-racemic drug was approved.

The GAO would have to report to Congress on whether these provisions have encouraged the development of new antibiotics and other drugs and prevented the timely entry of generics to the market.

## XVI. OTHER DRUG SAFETY PROVISIONS [TITLE IX]

### *A. Post-market Drug Safety Information for Patients and Providers*

FDAAA requires the creation of a website with links to drug safety information for patients and healthcare providers. The website will be easily searchable and contain information from government websites, including the United States National Library of Medicine's Daily Med, Medline Plus, and FDA sites. When the information is available and appropriate, the website will include labeling and package inserts, a link to the Medication Guide, a link to the registry and results data bank, the most recent FDA safety information and alerts, publicly available information about implemented RiskMAPs and REMS, and guidance documents and regulations related to drug safety.

The Secretary will provide access to summaries of known and serious side effects of drugs and a summary analyzing the adverse drug reaction reports received for a drug 18 months after a drug's approval or use by 10,000 individuals (whichever is later). The website will permit patients, providers, and drug sponsors to submit adverse event reports as well. The Secretary will also provide education materials about the proper means to dispose of expired or damaged medications.

On a regular basis, the Advisory Committee on Risk Communication will review and evaluate the types of information on the website, as well as recommend ways FDA could work with outside entities to help facilitate the distribution of risk communication information to patients and providers.

### *B. Action Package for Approval*

The law requires that the Secretary publish the action package for approval of an application on FDA's website. The action package will include documents generated by FDA for the application's review, documents pertaining to the format and content of the application, the labeling submitted by the applicant, a summary review with conclusions from all reviewing disciplines about the drug, the Division and Office Directors' decision document, and the name of the FDA officers or employees who participated in the decision to approve the drug (if they consent to have their names included).

### *C. Response to the IOM*

Within one year of enactment, the Secretary will have to

respond to the IOM report "The Future of Drug Safety--Promoting and Protecting the Health of the Public," updating the IOM on FDA's plan to respond to the report and including an assessment of how FDA implemented the IOM's recommendations. The Secretary's report would also assess FDA's implementation of the FDAAA requirement that the office responsible for reviewing a drug and the office responsible for post-approval safety work together to ensure compliance with REMS.

### *D. Database for Authorized Generic Drugs*

Under the law, the FDA Commissioner must publish a list of authorized generics on FDA's website. The list is to include the drug trade name, brand company manufacturer, and date the authorized generic entered the market. The Commissioner will update the list each quarter. The Commissioner will also notify the Centers for Medicare and Medicaid Services and the Federal Trade Commission when it first publishes the list.

## XVII. EFFECTIVE DATES

The law provides for the following effective dates:

a. The PDUFA Title is to be effective October 1, 2007. Beginning in fiscal year 2008, the Secretary must assess and collect fees for advisory review of drug television advertisements.

b. MDUFA's subtitle A is to be effective October 1, 2007.

c. The Conflicts of Interest Title is to be effective October 1, 2007.

d. The REMS section is to be effective 180 days after enactment.

e. The civil penalty and citizen petition provisions go into effect immediately.

*If you have any questions regarding FDAAA, please do not hesitate to contact us.*

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